POLICY FORUM

Grand Challenges in Global Health

H. Varmus, R. Klausner, E. Zerhouni, T. Acharya, A. S. Daar, P. A. Singer

On 26 January 2003, at the World Economic Forum in Davos, Switzerland, Bill Gates announced a $200-million medical research initiative—the Grand Challenges in Global Health—based on a century-old model, the grand challenges formulated by the mathematician David Hilbert (1). Hilbert's list of important unsolved problems in mathematics (1) has spurred major research innovations in the field. The Global Health initiative was proposed by the Bill & Melinda Gates Foundation (BMGF) on the assumption that, with greater encouragement and funding, contemporary science and technology could remove some of the obstacles to more rapid progress against diseases that disproportionately affect the developing world.

The efforts to identify Grand Challenges in Global Health relied on financial and administrative resources of two collaborating foundations, the BMGF and the Foundation for the National Institutes of Health (NIH); on a selection panel (scientific board) of 20 scientists and public health experts from 13 countries, including several from the developing world (2); and on the scientific community to supply ideas for challenges. In this Policy Forum, some of us involved in these events (H.V., R.K., and E.Z. as members of the Scientific Board's Executive Committee and P.A.S., T.A., and A.S.D. as scholars who provided support to the selection process) describe the deliberations that led up to this week's announcement of an initial list of Grand Challenges in Global Health (see table, page 399). We also outline the next steps that will be taken to fund research that addresses those challenges and plans to formulate additional grand challenges in subsequent years.

What Is a Grand Challenge?

On 1 May 2003, in a solicitation widely advertised in the developed and developing world, a grand challenge was described as "a call for a specific scientific or technological innovation that would remove a critical barrier to solving an important health problem in the developing world with a high likelihood of global impact and feasibility." Throughout the process of developing the grand challenges, the board struggled with how best to define them. A grand challenge is envisioned as distinct from a simple statement of one of the many "big problems" in global health, such as HIV/AIDS, malnutrition, the lack of access to medical care, or the lack of adequate resources. A grand challenge is meant to direct investigators to a specific scientific or technical breakthrough that would be expected to overcome one or more bottlenecks in an imagined path toward a solution to one or preferably several significant health problems. To satisfy this intent, a successful proposal would need to foresee a critical path of this type to get past a clearly defined roadblock. This formulation worked most effectively for those medical problems that are well enough understood to allow a description of what needs to be done, even if we do not yet know precisely how to do it. Thus, although the Grand Challenges initiative would ideally inspire unexpected and even radical solutions, the board also recognized the advantages of being able to envision solutions that have a high likelihood of being successful. The constraint of describing a "critical path past a bottle-neck" ruled out the broad field-building and exploratory research that usually underlies breakthroughs. Capacity building is another important approach (for example, increasing the number of biomedical research laboratories in the developing world, providing greater financial support for the study of global health or expanding professional training programs in global health) but beyond the purview of the program.

The scope of the initiative is broad, potentially encompassing many strategies for improving health through surveillance, prevention, detection, diagnosis, and treatment of diseases. Scientific disciplines underlying these strategies are also likely to be diverse, including immunology, microbiology, genetics, molecular and cellular biology, entomology, agricultural sciences, clinical sciences, epidemiology, population and behavioral sciences, and ecology and evolutionary biology. For example, control of pathogen-transmitting insect vectors is likely to make a big difference in reducing the incidence of diseases such as malaria and dengue fever that are common in the developing world. Chemical interventions, e.g., insecticides, have been thwarted by the emergence of insecticide resistance and constrained by environmental concerns. Two of the selected grand challenges are meant to encourage the development of novel chemical or genetic strategies for rendering mosquitoes incapable of transmitting disease agents, without adverse ecological or other environmental effects (3).

How Were Grand Challenges Selected?

The announcement of the Call for Ideas on 1 May 2003, was accompanied by a dissemination campaign that included a Web site (4), advertisements in scientific journals, and e-mail notifications, with the intent of engaging and eliciting ideas from scientists throughout the world. Between 1 May and 20 July, 1048 submissions were received from scientists and institutions in 75 countries. The large volume was gratifying but also required categorization according to topical content and the extent to which each submission met the criteria (4). The difference in number of proposals in various categories that met the criteria is reflected in the distribution of topics in the selected list of grand challenges.

The scientific board met on 17 and 18 August. To expedite discussion, the executive committee aggregated multiple, highly regarded, and closely related submissions into single proposals in advance of the meeting. The format chosen for presentation was the following: a brief statement of the background of the problem, followed by descriptions of the "roadblock" (the obstacle to progress) and the challenge itself, supplemented by lists of potential benefits, and, if appropriate, diseases or health conditions that are likely to be priority areas for study and application of findings. Each candidate was presented orally by two or more board members and then discussed by the full board. Wide participation was encouraged, so that ultimately all decisions were reached by oral consensus.

Questions raised during the discussions reflected the criteria that the board had proposed earlier, but they also illustrated the difficulties of defining grand challenges in global health. Does the proposal describe a difficult and discrete roadblock to progress? What is the likelihood that creative solutions are required and that grant proposals worthy of funding will be received to address it? Is there already substantial scientific activity aimed at solving the problem, which would make the intent of a grand challenge redun-

H. Varmus is the president and CEO of Memorial Sloan-Kettering Cancer Center, New York, NY 10021, USA. R. Klausner is the executive director of the Global Health Program, BMGF, Seattle, WA 98102, USA. E. Zerhouni is the director of the NIH, Bethesda, MD 20892, USA. T. Acharya, A. S. Daar, and P. A. Singer are at the University of Toronto Joint Centre for Bioethics, Toronto, Ontario, Canada M5G 1L4. Copyright of this work is retained by the authors.

dant? What are possible impacts on various diseases if the challenge is successfully met? Will envisioned advances be suitable for implementation in poorer parts of the world?

During, and especially after, the selection process, it became apparent that the challenges could be instructively grouped according to seven long-range goals (see table, below). None of the goals or selected grand challenges addresses a single disease. We believe this reflects successful pursuit of the original aim: to identify underlying scientific and technical problems that impede progress against multiple disorders.

A survey of the list, however, also reveals that both the goals and the selected challenges are heavily oriented toward the control of infectious diseases. This is so, in part, because infectious diseases account for the most profound disparities in health outcomes between the advanced and developing economies (5), and, in part, because the causes of infectious diseases are well known, making the formulation of technical and scientific obstacles to progress easier to envision than for poorly understood diseases. Nevertheless, the scientific board

recognizes and discussed at length the problems increasingly posed by chronic noncommunicable disorders and the importance of underlying living conditions, particularly access to clean water and adequate food, in large parts of the developing world. The board intends to pursue these issues by convening workshops on such topics and considering additional grand challenges in subsequent years.

Next Steps

Following the announcement of the Grand Challenges, the Foundation for NIH will issue a Request for Proposals (RFP) to address each of the challenges with grants of up to a total of $20 million over 5 years or less. How many grants will be made toward each challenge and how many of the 14 challenges will have funded grants will depend on the quality of the proposals and the available resources. Applications will be invited from anywhere in the world, from one or multiple institutions or countries in the developed or developing world and from nonprofit or for-profit institutions. The staff of the Foundation for NIH will oversee the ap-

plication and award processes, will encourage the participation of developing-country researchers, and will be available to advise about organizing interinstitutional or international consortia where appropriate. The application process [described in detail at (4)] will require the submission of a letter of intent by 9 January 2004. These letters will be reviewed by Foundation for NIH staff, members of the scientific board, and other selected experts; suitable candidates will then be asked to submit full applications, which will be due in June 2004. This vetting process will permit Foundation for NIH staff to discourage applications with little or no likelihood of success, and to assemble the appropriate number and type of review groups. Full applications will be evaluated by specially constituted review groups before the annual meeting of the scientific board, late in the summer of 2004. The scientific board will make recommendations to the Foundation for NIH, which expects to make awards around October 2004. Awards will likely exhibit a wide range of support levels and requirements for oversight.

The scientific board expects to continue to seek candidate challenges through new solicitations of ideas, the convening of workshops with invited speakers on defined topics, and continued discussion among members of the board. In the very design of its gift, the BMGF has challenged the world's scientists to produce a program that has the potential to improve the lives of many people.

GOALS AND GRAND CHALLENGES

To improve childhood vaccines:

GC 1: Create effective single-dose vaccines that can be used soon after birth;

GC 2: Prepare vaccines that do not require refrigeration;

GC 3: Develop needle-free delivery systems for vaccines.

To create new vaccines:

GC 4: Devise reliable tests in model systems to evaluate live attenuated vaccines;

GC 5: Solve how to design antigens for effective, protective immunity;

GC 6: Learn which immunological responses provide protective immunity.

To control insects that transmit agents of disease:

GC 7: Develop a genetic strategy to deplete or incapacitate a disease-transmitting insect population;

GC 8: Develop a chemical strategy to deplete or incapacitate a disease-transmitting insect population.

To improve nutrition to promote health:

GC 9: Create a full range of optimal bioavailable nutrients in a single staple plant species.

To improve drug treatment of infectious diseases:

GC 10: Discover drugs and delivery systems that minimize the likelihood of drug-resistant microorganisms.

To cure latent and chronic infections:

GC 11: Create therapies that can cure latent infections;

GC 12: Create immunological methods that can cure chronic infections.

To measure disease and health status accurately and economically in poor countries:

GC 13: Develop technologies that permit quantitative assessment of population health status;

GC 14: Develop technologies that allow assessment of individuals for multiple conditions or pathogens at point-of-care.

References and Notes

1. D. Hilbert, *Bull. Am. Math. Soc.* **8**, 437 (1901–02).
2. The members of the scientific board are Harold Varmus, Memorial Sloan-Kettering Cancer Center (Executive Committee, Chair); Richard Klausner, Bill & Melinda Gates Foundation (Executive Committee); Elias Zerhouni, National Institutes of Health (Executive Committee); Roy Anderson, Imperial College of the University of London; Mary Jane Cardosa, Universiti Malaysia Sarawak; Christine M. Debouck, GlaxoSmithKline Pharmaceuticals; Anthony S. Fauci, National Institute of Allergy and Infectious Diseases, NIH; William H. Foege, Bill & Melinda Gates Foundation; Julio Frenk, Minister of Health, Mexico; Nirmal Kumar Ganguly, Indian Council for Medical Research; Julie Louise Gerberding, U.S. Centers for Disease Control; Fotis C. Kafatos, European Molecular Biology Laboratory; Gerald Keusch, Fogarty International Center, NIH; Francis Kwesi Nkrumah, University of Ghana, Legon; Gustav Nossal, University of Melbourne; Odile Puijalon, Institut Pasteur; Yiming Shao, Chinese Center for Disease Control and Prevention; Peter A. Singer, University of Toronto Joint Centre for Bioethics; Florence Wambugu, A Harvest Biotech Foundation International; Yongyuth Yuthavong, Thai Academy of Science and Technology.
3. See supporting online material for further discussion.
4. www.grandchallengesgh.org.
5. World Health Organization, "Macroeconomics and Health: Investing in Health for Economic Development" (World Health Organization, Geneva, 2001).